Recommendations for the Use of Beta-Adrenergic Blockers in VA Patients with Chronic Heart Failure with Left Ventricular Systolic Dysfunction

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations.

According to the PBM-MAP The Pharmacologic Management of Chronic Heart Failure (HF), a beta-adrenergic blocker should be used in conjunction with an ACEI in all patients with stable Stage C HF* (patients with past or current HF symptoms and evidence of structural heart damage) with left ventricular (LV) systolic dysfunction, unless contraindicated (e.g., reactive airway disease, symptomatic bradycardia, advanced heart block without a pacemaker) or not tolerated.[1,2] Patients with HF are considered stable if they have minimal or no signs of fluid overload or volume depletion and not in an intensive care unit. It is also recommended that a beta-adrenergic blocker be initiated in patients post-myocardial infarction (MI), regardless of LV systolic dysfunction, and in patients with asymptomatic LV systolic dysfunction.[1,2]

Summary and Conclusions: ***The following conclusions are general recommendations. Local and/or VISN expertise may dictate the use of specific beta-adrenergic blockers for HF with LV systolic dysfunction.***

- Metoprolol XL has been shown to reduce morbidity and mortality in patients with HF. Due to the higher cost of this agent compared to some other beta-adrenergic blockers, it is recommended that metoprolol XL be used primarily for patients with HF (i.e., rather than angina, hypertension, or supraventricular tachyarrhythmias). Since metoprolol IR has yet to show a clear reduction in mortality, it is uncertain whether metoprolol IR provides similar benefit to metoprolol XL in patients with HF. Metoprolol XL provides an advantage over metoprolol IR in the ability to readily titrate patients with HF using the dosage forms available. It is also unknown if patients can be safely switched to metoprolol IR once titrated on metoprolol XL.
- Carvedilol has been shown to decrease morbidity and mortality in patients with NYHA class II-IV HF. Due to the high cost of carvedilol, this agent should be restricted to patients with HF (i.e., not prescribed for hypertension) as recommended in the PBM-MAP The Pharmacologic Management of Chronic Heart Failure and as stated on the VA National Formulary (VANF).
- According to a subgroup analysis of MERIT-HF, metoprolol XL may have positive outcomes in patients with more severe HF, as demonstrated with carvedilol in COPERNICUS. Although a slightly different patient population, bisoprolol has also been shown to reduce morbidity and mortality in patients with more severe HF.
- It is unknown if treatment with other available beta-adrenergic blockers (e.g., atenolol) provides the same mortality benefit as seen with the agents used in large published clinical trials (i.e., bisoprolol, carvedilol, metoprolol XL). Use of beta-adrenergic blockers other than those with demonstrated efficacy in reducing morbidity and mortality in patients with HF should be at the discretion of the clinician.
- The Carvedilol Or Metoprolol European Trial (COMET) attempted to answer the question of whether to use a selective beta-adrenergic blocker (e.g., metoprolol) versus a non-selective agent with alpha-adrenergic blocking and antioxidant effects (e.g., carvedilol). The results of this trial showed that treatment with carvedilol had a greater reduction in mortality when compared to treatment with metoprolol IR. There continues to be debate as to whether the dose of metoprolol IR may have influenced the difference in results.
- Whether there is a difference in efficacy with the various beta-adrenergic blockers depending on patient demographics has not been established at this time. A recent evidence report concluded that the benefit of beta-blockers is evident for both men and women with symptomatic HF and that black patients should derive the same benefits as white patients when treated with bisoprolol, carvedilol, or metoprolol.

*Treatment of chronic heart failure (HF) is based upon the classification of HF into four stages by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines: Stage A includes patients who are at high risk for developing HF, but do not have structural heart disease; Stage B are patients who do have structural damage to the heart, but have not developed symptoms; Stage C refers to patients with past or current HF symptoms and evidence of structural heart damage; and Stage D includes patients with end-stage disease, requiring special interventions. It is the intent of the ACC/AHA recommendations to be used in conjunction with the New York Heart Association (NYHA) functional classification that estimates the severity of disease based on patient symptoms.

Recommendations for Titration in Patients with HF:

Use with caution in patients with systolic dysfunction; initiate only if clinically stable HF, unless contraindicated or not tolerated

Beta-blocker	Strength	Titration	Target Dose[a]
Bisoprolol	5mg (scored), 10mg film-coated tablets	• Initial dose 1.25mg qd • Increase 1.25mg weekly until 5mg qd, then 2.5mg every 4 weeks to target dose *CIBIS II excluded patients with SBP < 100 mmHg and HR < 60 bpm*	10mg qd
Carvedilol	3.125mg (not scored), 6.25mg, 12.5mg, 25mg scored tablets	• Initial dose 3.125 mg bid (carvedilol should be administered with food to reduce orthostatic hypotension; consider separating the ACEI, adjusting dose of diuretic, or temporary ACEI dose reduction if dizziness occurs) • Dose should be doubled at a minimum of every 2 weeks to the target dose *COPERNICUS and US Carvedilol excluded patients with SBP < 85 mmHg and HR < 68 bpm; manufacturer recommends ↓ dose if HR < 55 bpm*	25 mg bid (50mg bid ≥ 85 kg; titrate with caution)
Metoprolol	50mg, 100mg scored tablets	• Initial dose 6.25 mg qd/bid (low dosages of metoprolol are not commercially available, although various methods of titration have been used;[b] • Double dose every 2 weeks until target dose achieved *MDC excluded patients with SBP < 90 mmHg and HR < 45 bpm; discontinue if SBP < 90 mm Hg or HR < 40 bpm per manufacturer*	50-75mg bid
Metoprolol XL	25mg, 50mg, 100mg, 200mg scored, film-coated tablets	• Initial dose 12.5mg qd ≥ NYHA class III HF; 25mg qd < NYHA class III HF • Double dose every 2 weeks until target dose *MERIT-HF excluded patients with SBP < 100 mmHg*	200mg qd
Atenolol[c]	25mg, 50mg (scored), 100mg tablets	• Initial dose 12.5mg bid • Increase by 12.5mg per week for the next 2 weeks, then by 25mg per week as tolerated to target dose *Did not proceed with titration unless SBP ≥ 90 mm Hg and HR ≥ 60 bpm*	50-100mg divided qd-bid

[a] Or highest dose tolerated; beta-adrenergic blockers should not be abruptly discontinued

[b] Eichhorn EJ, Bristow MR. Practical guidelines for initiation of beta-adrenergic blockade in patients with chronic heart failure. Am J Cardiol 1997;79:794-8

[c] Limited outcome data (trial of 100 patients), although still being used

Beta-blocker Comparison

Beta-blocker:	Atenolol	Bisoprolol	Carvedilol	Metoprolol IR	Metoprolol XL
VA National Formulary	X		X[a]	X	X[a]
FDA Indication					
Heart Failure			X		X
Angina	X			X	X
Hypertension	X	X	X	X	X
Outcome data in HF		X	X		X
$Beta_1$ cardioselective	X	X		X	X
Alpha-blocker			X		
Antioxidant			X		
QD regimen	X[b]	X			X
Cost	$	$$	$$$	$	$$

[a] Restricted to PBM-MAP The Pharmacologic Management of Chronic Heart Failure

[b] Twice daily regimen used in clinical trial

Beta-blockers Prices

Beta-blocker	Strength/Regimen	Price per tablet	Estimated $ for Titration	Maintenance ($/month)
Bisoprolol	5mg qd	$0.6037	$34.54 (8 wks)	$18.11
	10mg qd	$0.6557		$19.67
Carvedilol	3.125mg bid	$0.9619	$107.75 (8 wks)	$57.71
	6.25mg bid	$0.9629		$57.77
	12.5mg bid	$0.9623		$57.74
	25mg bid	$0.9615		$57.69 ($115.38 50mg bid if ≥ 85kg)
Metoprolol	50mg bid	$0.0136	$0.72 (8 wks)	$0.82
	100mg bid	$0.0248		$1.49
Metoprolol XL	25mg qd	$0.3329	$18.65 (8 wks)	$9.99
	50mg qd	$0.3329		$9.99
	100mg qd	$0.5002		$15.01
	200mg qd	$0.9958		$29.87
Atenolol	25mg qd-bid	$0.0192	$0.99 (8 wks)	$0.58-1.15
	50mg qd-bid	$0.0157		$0.47-0.94
	100mg qd	$0.0265		$0.80

Survival Data in Heart Failure

Trial	Methods	Results	Comments
CIBIS II[3] R, DB, PC	2647 pts; mean age 61 (22-80) yrs 50% CAD NYHA class: 83% III, 17% IV Mean EF: 27.5% F/U: mean 1.3 yrs Bisoprolol (majority 10mg/d) Addnl tx: ACEI, diuretics, 53% digoxin PEP: all-cause mortality	Bisoprolol ↓ PEP 34% (P<0.0001), ARR 5.5% ↓ CV deaths (P=0.0049) 42% ↓ sudden death (P=0.0011) ↓ hosp (P=0.0006) NNT (PEP): 18.2	Trial stopped early due to improved survival; subgroup analysis, class IV did not benefit as much, but not sig different
MERIT-HF[4] R, DB, PC	3991 pts; mean age 63.9 yrs Sx HF; 62% ischemic etiology NYHA class: 41% II, 56% III, 3.4% IV Mean EF: 28% F/U: mean 12 months Metoprolol XL (mean 159 mg/d) Addnl tx: ACEI, diuretics, 2/3 digoxin PEP: all-cause mortality	Metoprolol XL ↓ PEP 34% (P=0.00009), ARR 3.6% 41% ↓ sudden death; 49% ↓ death from worsening HF NNT (PEP): 27.8	Study stopped early because of mortality benefit
U.S. Carvedilol[5] (Survival) R, DB, PC	1094 pts; mean age 58 yrs ischemic or nonischemic etiology NYHA class: 53% II, 44% III, 3% IV Mean EF: 23% Median F/U: 6.5 months Carvedilol (mean 45 ± 27mg/d) Addnl tx: ACEI, loop diuretic, digoxin PEP: death or hosp due to CV reasons	Carvedilol ↓ PEP 38% (P<0.001), ARR 8.8% 65% ↓ risk of death (P<0.001), ARR 4.6% 27% ↓ risk CV hosp (P=0.036) NNT (PEP): 11.4 NNT (death): 21.7	Trial stopped early due to sig improved survival with carvedilol
COPERNICUS[6] R, DB, PC	2289 pts; mean age 63 yrs ischemic or nonischemic etiology Severe HF (≥ 2 months dyspnea/fatigue at rest or minimal exertion, EF < 25%) Mean EF: 19.9% Median F/U: 10.4 months Carvedilol (mean 37 mg/d) Addnl tx: ACEI/AIIRA, diuretic, digoxin PEP: all-cause mortality	Carvedilol ↓ PEP 35% (P=0.0014), ARR 5.5% 24% ↓ risk combined death or hosp (P<0.001) NNT(PEP): 18.2	Trial stopped early due to sig improved survival with carvedilol. Annual placebo mortality of 19.7% per patient year of follow-up.
COMET[7] R, DB, PG	3029 pts; mean age 62yrs Sx HF, previous CV admission w/in past 2 yrs > 50% ischemic etiology NYHA class: 48-49% II, 47-48% III, 3-4% IV Mean EF: 26% Median F/U: 58 months Carvedilol (mean 41.8 ± 14.6mg/d) Metoprolol IR (mean 85 ± 28.9mg/d) Addnl tx: ACEI, diuretic PEP: all-cause mortality	Carvedilol ↓ PEP 17% vs. metoprolol (P=0.017), ARR 5.6% Composite all-cause mortality or all-cause hosp (P=0.122) NNT(PEP): 17.7	78% metoprolol 50mg bid (target dose) 75% carvedilol 25mg bid (target dose)

ACEI=angiotensin-converting enzyme inhibitor; Addnl tx=additional treatment; AIIRA=angiotensin II receptor antagonist; ARR=absolute risk reduction; CAD=coronary artery disease; CV=cardiovascular; DB=double-blind; EF=ejection fraction; F/U=follow-up; HF=heart failure; hosp=hospitalizations; NNT=number needed to treat; PC=placebo-controlled; PEP=primary endpoint; PG=parallel group; R=randomized

Meta-analyses of the beta-adrenergic blocker trials show a reduction in mortality of approximately 30 to 35%.[8-11] Prior to the publication of MERIT-HF and CIBIS II, a trial with metoprolol IR (Metoprolol in Dilated Cardiomyopathy, or MDC) and one with bisoprolol (Cardiac Insufficiency Bisoprolol Study, or CIBIS) were conducted. These two trials did not demonstrate a statistically significant improvement in the primary endpoints. It should be noted in the MDC trial that after twelve months, the primary endpoint of death or need for heart transplant was reduced 34% in patients on metoprolol IR at a mean dose of 108mg/d (P=0.058). Although there was not a statistically significant difference in the combined endpoint, the need for heart transplant was significantly lower in patients on metoprolol (P=0.001). This trial included 343 patients (mean age 49 years) with nonischemic dilated cardiomyopathy, 94% who were in NYHA class II or III HF with a mean left ventricular ejection fraction (LVEF) of 22%. Patients on metoprolol IR experienced a significant improvement in LVEF, exercise capacity, and quality of life.[12] In CIBIS, 641 patients (mean age 60 years) with NYHA class III (95%) or IV (5%) HF (mean LVEF 25.8%) of ischemic or nonischemic etiology, were followed for a mean of almost 2 years. Patients received a mean dose of bisoprolol 3.8 ± 0.2mg/day, with 51% on 5mg/day. Bisoprolol decreased total mortality (primary endpoint) by 20%, however this did not achieve statistical significance (P=0.22). Improvement of at least one NYHA functional class was seen in 21% of bisoprolol

patients and 15% of placebo patients (P<0.03). Fewer patients required hospitalization for worsening HF (P<0.01).[13] It should be pointed out that lower doses were used in these trials compared to MERIT-HF and CIBIS-II and the study population was not as large.

In a subgroup analysis of MERIT-HF, 795 patients with NYHA class III or IV HF with a LVEF < 25% who received placebo or metoprolol XL were compared. Similar to COPERNICUS, the mean baseline LVEF was 19.1% and the annual mortality for patients in the placebo group was 19%. Patients randomized to metoprolol XL experienced a decreased risk of total mortality (39%, P=0.0086), death due to worsening HF (55%, P=0.015), hospitalization due to worsening HF (45%, P<0.0001), and combined all-cause mortality or all-cause hospitalization (29%, P=0.0012) compared to placebo. [14]

As with COPERNICUS and CIBIS-II, the Beta-Blocker Evaluation of Survival Trial (BEST) evaluated patients with more severe HF. BEST enrolled 2708 patients with NYHA class III (92%) or IV (8%) HF and a LVEF $\leq$ 35% (mean LVEF 23%) who were randomized to placebo or bucindolol (not available in the U.S.). The trial was discontinued after a mean follow-up of 2 years due to the evidence from BEST and other trials that beta-adrenergic blockers are beneficial in patients with HF. Upon termination of BEST, there was not a significant difference in the primary endpoint of mortality between the two groups of patients (adjusted P=0.13). The secondary endpoint of cardiovascular death was lower in patients on bucindolol (P=0.04). There was a decreased proportion of patients with HF related hospitalizations (P<0.001) and with the combined endpoint of death or heart transplant (P=0.04). After subgroup analysis, there was a significant survival benefit in nonblack patients (P=0.01) but not in black patients (P=0.27). There was also a trend toward improved survival in patients with less severe HF (P=0.05 in patients with LVEF > 20%). The authors stated that due to the small number of patients with NYHA class IV HF, definitive conclusions could not be made in these patients.[15]

The difference in response in black compared to nonblack patients in BEST is contrary to findings from a retrospective comparison of patients enrolled in the U.S. Carvedilol Heart Failure Study where the benefit of carvedilol was not statistically significantly different between black and nonblack patients.[16] A recent meta-analysis by the U.S. Department of Health and Human Services reported the estimate of pooled random-effects of the relative risk for mortality in black patients to be 0.67 (0.39-1.16) compared to 0.63 (0.52-0.77) for white patients. Results were similar for the pooled estimates from the hazard ratio analysis. The evidence report to address the potential difference in mortality of beta-adrenergic blockers depending on race concluded that black patients should derive the same benefits as white patients when treated with bisoprolol, carvedilol, or metoprolol (the results of BEST were not included in the pooled analysis).[17]

The use of a beta-adrenergic blocker has also been studied in patients with a LVEF $\leq$ 40% post-MI. The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial randomized 1959 patients to carvedilol or placebo. There was not a statistically significant difference in the primary endpoint of all-cause mortality or hospital admission for cardiovascular problems (originally a prespecified secondary endpoint). The original primary endpoint of all-cause mortality (changed to co-primary endpoint due to inadequate sample size and power) was lower (but not statistically significant based on α=0.005 for all-cause mortality alone) in patients on carvedilol compared to placebo [hazard ratio 0.77 (0.60-0.98), P=0.03].[18]

The question of whether to use a selective beta-adrenergic blocker (e.g., bisoprolol or metoprolol) versus a non-selective agent with alpha-adrenergic blocking and antioxidant effects (e.g., carvedilol) remains controversial.[7,19-23] Although COMET demonstrated a statistically significant improvement in survival with carvedilol compared to metoprolol IR, it is unknown whether there is a difference between carvedilol and metoprolol IR (or XL) when prescribed at the recommended target doses. Since metoprolol XL was not available at the time of enrollment in COMET, metoprolol IR was selected as the comparator to carvedilol, at doses that were expected to result in comparable beta-blockade. Much of the discussion about the results of COMET includes the difference in target dose and effect on resting heart rate. The dose of carvedilol used in COMET achieved a similar reduction in heart rate as seen in U.S. Carvedilol (i.e., 13 beats per minute). The mean dose of metoprolol IR used in COMET was less than the mean dose in MDC (i.e., 85 vs. 108mg/d), and resulted in less of a decrease in heart rate (i.e., 11.7 vs. 15 beats per minute). The mean dose in MERIT-HF was 159mg/d and achieved a reduction in heart rate of 14 beats per minute.[4,5,7,12,23] Whether these factors had an influence on the results is unknown. In addition, whether metoprolol IR provides equivalent benefits as seen with metoprolol XL is undetermined.[24-26] Very few trials with beta-adrenergic blockers that are available in the U.S. other than bisoprolol, carvedilol, or metoprolol have been published.[27,28] It is therefore unknown if treatment with other beta-adrenergic blockers would provide the same benefits as seen with the agents that have demonstrated a reduction in mortality in patients with heart failure.

References:

[1] The pharmacologic management of chronic heart failure. Washington, DC: Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Veterans Health Administration, Department of Veterans Affairs; April 2001; Updated December 2002. PBM-MAP Publication No. 00-0015.

[2] Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). 2001. American College of Cardiology Web site. Available at:http://www.acc.org/clinical/guidelines/failure/hf_index.htm

[3] CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.

[4] MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.

[5] Packer M, Bristow MR, Cohn JN, et al for the U.S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349-55.

[6] Packer M, Coats AJS, Fowler MB, et al. for the Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.

[7] Poole-Wilson PA, Swedberg K, Cleland JGF, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomized controlled trial. Lancet 2003;362:7-13.

[8] Doughty RN, Rodgers A, Sharpe N, MacMahon S. Effects of beta-blocker therapy on mortality in patients with heart failure: a systematic overview of randomized controlled trials. Eur Heart J 1997;18:560-5.

[9] Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. J Am Coll Cardiol 1997;30:27-34.

[10] Lechat P, Packer M, Chalon S, et al. Clinical effects of β-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. Circulation 1998; 98: 1184-91.

[11] Brophy JM, Joseph L, Rouleau JL. β-blockers in congestive heart failure: a Bayesian meta-analysis. Ann Intern Med 2001;134:550-60.

[12] Waagstein F, Bristow MR, Swedberg K, et al for the Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet1993;342:1441-6.

[13] CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure: The Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1994;90:1765-73.

[14] Goldstein S, Fagerberg B, Hjalmarson A, et al for the MERIT-HF Study Group. Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. J Am Coll Cardiol 2001;38:932-8.

[15] The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344:1659-67.

[16] Yancy CW, Fowler MB, Colucci WS, et al. for the U.S. Carvedilol Heart Failure Study Group. Race and response to adrenergic blockade with carvedilol in patients with chronic heart failure. N Engl J Med 2001;344:1358-65.

[17] Pharmacologic management of heart failure and left ventricular systolic dysfunction: effect in female, black, and diabetic patients, and cost-effectiveness. U.S. Department of Health and Human Services, 2003; Evidence Report/Technology Assessment No. 82.

[18] The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomized trial. Lancet 2001;357:1385-90.

[19] Packer M, Antonopoulos GV, Berlin JA, et al. Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: results of a meta-analysis. Am Heart J 2001;141:899-907.

[20] Adams KF Jr. Which β-blocker for heart failure? Am Heart J 2001;141:884-8.

[21] Yancy CW. Clinical trials of β-blockers in heart failure: a class review. Am J Med 2001;110:7S-10S.

[22] Maack C, Elter T, Nickenig G, et al. Prospective crossover comparison of carvedilol and metoprolol in patients with chronic heart failure. J Am Coll Cardiol 2001;38:939-46.

[23] Dargie HJ. Beta-blockers in heart failure. Lancet 2003;362:2-3.

[24] Kukin ML, Mannino MM, Freudenberger RS, et al. Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure. J Am Coll Cardiol 2000;35:45-50.

[25] Egstrup K, Gundersend T, Härkönen R, Karlsson E, Lundgren B. The antianginal efficacy and tolerability of controlled-release metoprolol once daily: a comparison with conventional metoprolol tablets twice daily. Eur J Clin Pharmacol 1988; 33 (Suppl):S45-9.

[26] Prakash A, Markham A. Metoprolol: a review of its use in chronic heart failure. Drugs 2000;60:647-78.

[27] Sturm B, Pacher R, Strametz-Juranek J, et al. Effect of β1 blockade with atenolol on progression of heart failure in patients pretreated with high-dose enalapril. Eur J Heart Fail 2000;2:407-12.

[28] Leung WH, Lau CP, Wong CK, et al. Improvement in exercise performance and hemodynamics by labetalol in patients with idiopathic dilated cardiomyopathy. Am Heart J 1990;119:884-90.

Prepared by: E. Furmaga, Pharm.D.
Reviewed by: P. Glassman, M.B.B.S. M.Sc., R. Hariman, M.D.